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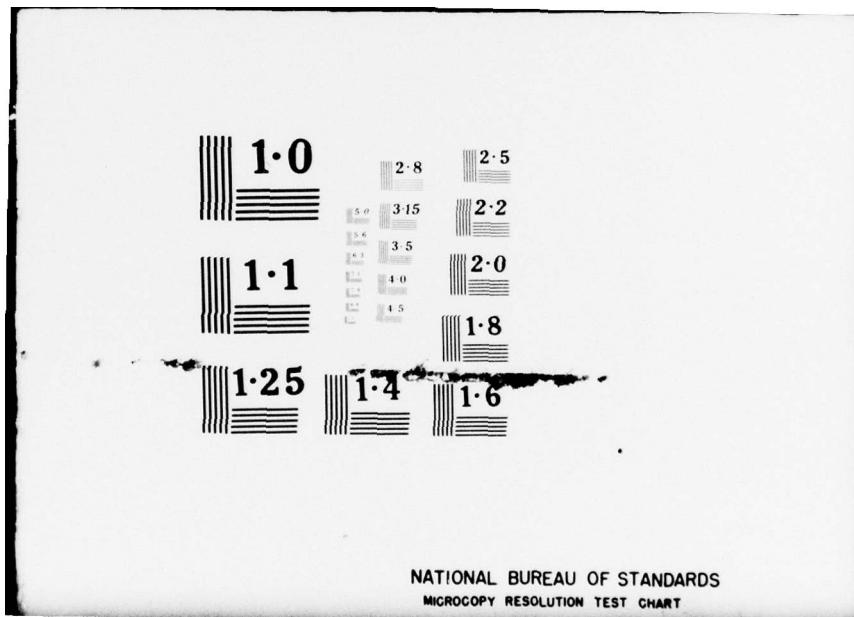
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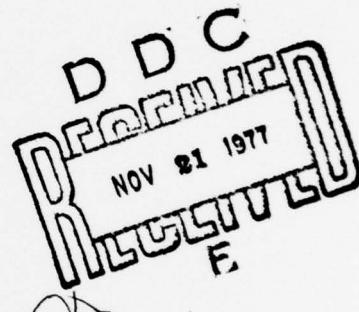
REPORT NUMBER 2

Phase I Clinical Testing
Antimalarial Drugs

Annual Report

Richard C. Reba, M.D.

Date October 1977



Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D.C. 20314

Contract No. DAMD 17-75-C-5036

BIO-MED, Inc.
110 Irving Street, N.W.
Washington, D.C. 20010

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This report includes work performed under Contract DAMD 17-75-C-5036 from February, 1976 through January, 1977.		
The 52-week, safety and tolerance test administration of 500 mg mefloquine weekly continues. Four of the 5 groups (10 each) have completed the drug administration interval. The only possible drug related adverse reaction observed was the occurrence of telogen effluvium (temporary scalp hair loss) in 2 subjects receiving drug.		

20. Abstract (Continued)

Dosing will be completed for the last group in May, 1977.

Three additional acute studies involving oral mefloquine administration were completed and reports submitted. These studies revealed gastrointestinal intolerance at the 1750 mg dose level of both (E-443 - B-512) formulations. Following administration of the newer formulation B-512, transient nausea and diarrhea occurred in some subjects receiving 1000 mg and all subjects receiving 1500 mg mefloquine. No other intolerance was observed at these dose levels.

WR 184,806·H₃PO₄ studies were extended: serum and urine collections for pharmacokinetics following single oral dose administration of 250, 500, and 1000 mg doses have been completed.

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A new agent WR 180,409·H₃PO₄, a substituted pyridine methanol, underwent initial clinical testing using single rising dose levels. Intolerance manifested by combinations of nausea, emesis, dizziness, decrease in mental acuity, and insomnia occurred in most subjects at the 1000 mg dose and both subjects receiving 1500 mg WR 180,409·H₃PO₄. The symptoms were mild, of less than 48 hours duration, and not associated with physical or laboratory abnormalities attributed to drug.

Finally, projects for the coming year have been scheduled in collaboration with the clinical monitor and his staff.



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by other authorized documents.

SUMMARY

BIO-MED, Inc. continued Phase I Clinical Testing of antimalarial drugs during this second contract year. The drugs were developed by the antimalarial drug program of the U.S. Army Medical Research and Development Command. Testing was performed at the Washington Hospital Center in Washington, D.C. under contract DAMD-17-75-C-5036.

The 52-week safety and tolerance test administration of 500 mg mefloquine weekly has continued throughout the year. Four of the 5 groups (10 subjects per group) have completed the drug administration interval. The only possibly drug related adverse reaction observed to date was the occurrence of telogen effluvium in 2 subjects receiving drug. Telogen effluvium is a reversible increase in hair loss which may be drug related or related to emotional tension. When drug related, reversal is apparent 2-3 months after discontinuing drug administration. At present it cannot be stated whether the increase rate of hair loss observed in the 2 subjects was drug related. Additional preclinical studies of mefloquine were reported in which epididymal changes occurred in rats receiving high dose, prolonged daily administration of mefloquine. Following appropriate consultation it was decided to inform the subjects of the findings and to offer sperm evaluation to all subjects. All subjects declined the offer and none discontinued study because of the report.

Studies of WR 184,806·H₃PO₄, another substituted quinoline methanol were continued. During the initial contract year it was demonstrated that the drug was well tolerated up to 1000 mg as a single dose and 400 mg every 8 hours for 72 hours in multiple oral doses. This year pharmacokinetic studies following oral administration of 250, 500, and 1000 mg doses were completed. Drug assay is being performed by the Department of Pharmacology at Walter Reed Army Institute of Research: the serum and urine concentration levels are not yet available to BIO-MED. It is noted that as in the previous study at the 1000 mg dose level, mild transient symptoms of light-headedness occurred. In this instance symptoms occurred in 2 of the 5 subjects receiving the 1000 mg dose.

Three additional acute studies involving the oral administration of mefloquine were completed and reports submitted: the first study was initiated to determine the top tolerated single oral dose of the drug. The initial dose level selected was 1.75 grams which produced temporary nausea, vomiting, abdominal cramps, and watery diarrhea in both subjects receiving the drug. The intolerance to this dose level as compared to tolerance at higher dose levels in previous studies was attributed to the use

of a new formulation (Lot B-512) in place of the formulation (Lot E-443) used in previous studies. It was also found when mefloquine (Lot B-512) formulation was administered as a single dose repeated 7 days later that intolerance was minimal and inconsistent at the 1000 mg dose level but constant following each administration at the 1500 mg dose level. The manifestations of intolerance included mild diarrhea persisting for $\frac{1}{2}$ to 3 hours, occasional nausea and in one instance a single emesis. Additionally, a cross-over study to compare the E-443 formulation with the B-512 formulation was performed at a 1750 mg single oral dose level. Gastrointestinal intolerance occurred with both formulations at this dose level although the E-443 formulation was better tolerated than the B-512 formulation. The gastrointestinal symptoms were mild and transient as had been observed in previous studies. Light-headedness occurred in 3 subjects. In all instances it was mild but in 1 subject persisted for 5 days following each drug administration. No other potentially adverse reactions were observed. Results of drug assays are not yet available to BIO-MED, Inc.

A substituted pyridine methanol designated WR 180,409-H₃PO₄ underwent initial clinical testing using single rising oral dose levels in a double-blind study. Thirteen of the 22 subjects administered drug had symptoms considered possibly drug related. The symptoms included nausea, emesis, light-headedness, and mental fuzziness. The pattern of symptomatology suggests that mild intolerance occurred at the 1000 mg level. Intolerance was consistent at the 1250 mg level and most marked at the 1500 mg dose. Even at this dose level the symptoms were nonincapacitating and did not exceed 30 hours duration.

Finally, the BIO-MED staff has collaborated with the clinical monitor and his staff in scheduling projects for the coming contract year. The studies will include clinical testing of drugs already subjected to initial testing as well as testing of new antimalarial agents.

FOREWORD

Under terms of the contract, Phase I Clinical Testing of antimalarial drugs were performed at the Washington Hospital Center. All protocols were processed by the contractor's Organizational Review and Human Subject (Human Use) Committees prior to submission to the Washington Hospital Center Research Committee.

All protocols were processed and approved by the Washington Hospital Center prior to implementation. The Washington Hospital Center is approved for performance of clinical research by the Department of Health, Education, and Welfare. (DHEW Assurance No. GO 180)

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OBJECTIVES

General: To continue Phase I Clinical Testing of antimalarial drugs at the Washington Hospital Center using methodology providing maximum protection for the health and welfare of participating subjects.

Specific:

1. To continue the chronic safety and tolerance study of mefloquine, a quinoline methanol with demonstrated efficacy for prevention and therapy of multi-drug resistant *P. Falciparum* malaria. The study includes weekly administration of 500 mg drug or placebo for 52 weeks to 50 subjects.
2. To expand the acute studies of mefloquine including determination of the top tolerated dose, the safety and tolerance of repeating a single oral dose 7 days after the first administration, to compare formulation E-443 with formulation B-512 and to obtain pharmacokinetic data following single oral dose administration.
3. To study the pharmacokinetics of WR 184,806·H₃PO₄ following single oral dose administration.
4. To determine the safety and tolerance of WR 180,409·H₃PO₄ administered as a single oral dose.

METHODS AND RESULTS

1. Mefloquine 52 Week Study:

Four of the 5 groups (10 each) have completed drug administration. No serious adverse reactions have been observed and the only potential adverse reaction is temporary increase of scalp hair loss in 2 subjects receiving drug. All subjects are being monitored for this occurrence. It is projected that the final loss of subjects from study will be less than 30% which is considered remarkable considering a study interval of over 1 year for each participating subject.

2. Mefloquine Extension of Acute Studies:

These studies have been described in some detail in the summary of this report. The study summaries are attached and indexed in the table of contents. The observation which was not expected is that intolerance to the new formulation B-512 is primarily gastrointestinal and occurs at a lower dose level than expected from previous studies done elsewhere utilizing the original formulation designated E-443. Drug assay results are not yet available to BIO-MED to compare absorption and pharmacokinetics of B-512 and E-443.

3. Pharmacokinetics Study, WR 184,806·H₃PO₄:

The method used included administration of single oral doses of 250, 500, and 1000 mg of the drug with venous blood specimens drawn at appropriate time intervals to permit pharmacokinetic analysis. Additionally, 24-hour urines were collected before and for 72 hours following drug administration. No significant clinical adverse effect occurred during the study. Drug assay results are not yet available for interpretation and conclusions.

4. Acute Safety and Tolerance, WR 180,409·H₃PO₄:

A double-blind method was used for the administration of single oral doses of this drug in rising dose levels. The study summary of the report is attached and indexed in the table of contents. Intolerance occurred inconsistently at the 1000 mg dose level but was constant at the 1500 mg dose level. Intolerance was manifested by combinations of nausea, emesis, dizziness, decrease in mental acuity, and insomnia. The symptoms were mild, of less than 48 hours duration, and not associated with physical or laboratory abnormalities attributed to drug administration.

CONCLUSIONS

The second contract year has been characterized by routine application of the most efficient methods developed during the initial year.

The benefits of maintaining a close relationship between the Human Use Committee members and study subjects is apparent in the low dropout rate in the 52-week study and excellent compliance in all studies.

The development and administration of a new mefloquine formulation (B-512) generated the need for additional studies many of which have been completed.

The step-by-step testing of new drugs in an orderly and deliberate manner with continuous participation of the clinical monitor decreases the potential for exposure to undue risk for subjects as well as assuring a high caliber scientific product.

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FINAL REPORT EXPERIMENT NO. 3: WR 142,490·HCl SHORT TERM SAFETY AND TOLERANCE Single Dose Levels

STUDY SUMMARY

INTRODUCTION:

WR 142,490·HCl is an investigative quinoline methanol which has undergone extensive tolerance and efficacy studies in human subjects. As of 23 July 1974, 112 volunteers have received various doses of WR 142,490. A 2 by 2 rising dose double blind Phase I tolerance study in volunteers has been performed to a maximum dose of 2 gm administered as a single dose. Occasional subjects at this dose of the drug complained of transitory "dizziness". This included subjects receiving placebos as well as subjects receiving test drug. There were no physical abnormalities detected and laboratory tests were normal in these subjects.

The purpose of this study was to determine the top tolerated single oral dose of WR 142,490.

METHODS:

Subject Selection:

Male candidates 21 to 45 years of age were selected from applicants for temporary employment as study subjects.

Drug Administration:

A double blind method was used. The initial dose level was 1.75 grams. Drug lots used and dose levels are on file.

Clinical and Laboratory Evaluations:

The schematic table detailing the sequence of tests during each study interval is on file. Serial comprehensive medical evaluation including physical, biochemical and hematologic testing was performed on each subject.

RESULTS:

General:

Intolerance occurred in both subjects receiving WR 142,490·HCl at the initial dose level of 1.75 gm. Therefore, the study was suspended pending further investigation.

Symptoms and Physical Findings:

Both subjects who ingested WR 142,490·HCl at the first dose level of 1.75 gm developed symptoms after drug administration. Both subjects ingesting placebo were asymptomatic throughout the study.

One subject experienced nausea and mild epigastric discomfort 30 minutes after drug ingestion followed 30 minutes later by a loose watery stool. The nausea and abdominal discomfort lessened after passage of a 2nd watery stool 2½ hours after drug ingestion, but persisted for a total duration of 3½ hours. The subject then felt well until 24 hours after drug ingestion when, following breakfast, he had a single unexpected emesis. Thereafter he remained asymptomatic.

The other subject developed mild abdominal cramping followed by watery diarrhea 30 minutes after drug ingestion. During the following 5 hours the subject had another six watery stools and thereafter was asymptomatic.

The observations upon physical examination remained unchanged in both subjects during and after the symptoms noted.

Clinical Laboratory Studies:

Hematologic and Biochemical: There were no significant alterations attributed to drug ingestion.

Urinalysis: No abnormalities were detected.

Electrocardiography and Phototoxicity Testing: No rhythm strip electrocardiographic changes or phototoxicity were produced under conditions of the study.

Individual Summaries: Summaries for each subject are on file.

CONCLUSION:

The administration of 1.75 gm WR 142,490·HCl under conditions of this study was associated with temporary nausea,

vomiting, abdominal cramps and watery diarrhea. The intolerance to this dose level as compared to tolerance at higher dose levels in previous studies is attributed to the use of a new formulation (Lot B512) in place of the formulation (Lot E443) used in the previous studies.

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ADDENDUM TO EXPERIMENT 3 WR 142,490·HCl SHORT TERM SAFETY AND TOLERANCE Clinical Evaluation of Two Formulations

STUDY SUMMARY

INTRODUCTION:

WR 142,490·HCl, Mefloquine Hydrochloride, is an investigational quinoline methanol which has been shown to be effective in the treatment and prophylaxis of humans with chloroquine resistant strains of Plasmodium falciparum.

The purpose of this study was to determine the relative tolerance and bioavailability of two formulations of the antimalarial drug mefloquine HCl (WR 142,490·HCl) administered orally to healthy subjects.

Phase I testing, in volunteers, showed that the drug was well tolerated in single doses up to 2,000 mg. Transient light-headedness occurred in both dosed and control subjects at single oral doses of 1,500 and 1,750 mg but not at 2,000 mg. An additional study was designed to extend the Phase I tolerance study to 2,500 mg in a rising dose double blind study. This study was initiated at an oral dose of 1,750 mg, a previously tolerated dose, because the study was to be conducted in a different study population using a more rapidly dispersing coated tablet formulation manufactured by INTERx, Lawrence, Kansas (Lot B512) instead of the previous tablet formulation manufactured by Lafayette Pharmacal, Inc., Lafayette, Indiana (Lot E443). Gastrointestinal intolerance occurred in two subjects at the initial 1,750 mg dose manifested by watery diarrhea 30-45 minutes after the drug was administered and continuing for 3 to 4 hours. A further study, Experiment No. 4 entitled "WR 142,490·HCl Safety and Tolerance, Repetitive Curative Dose Levels" was designed and conducted to test the tolerance of the INTERx formulation WR 142,490·HCl when the drug was administered orally on Days 1 and 7. Single repetitive oral doses of 1,000, 1,250, and 1,500 mg were given to 3 groups of subjects using a 2 x 2 rising double blind method. In this study, diarrhea starting 30 to 60 minutes after dosing and lasting $\frac{1}{2}$ -3 hours, occurred in all four subjects receiving the 1,250 and 1,500 mg dose. In the 2 subjects ingesting 1,500 mg, diarrhea occurred after both administrations. Diarrhea occurred after both doses of 1,250 mg in one subject but only after the first dose in the other subject.

An accurate chemical analysis for mefloquine in serum specimens is now available. The analysis is currently in use in the laboratories of the Department of Pharmacology, Division of Medicinal Chemistry at Walter Reed Army Institute of Research. Therefore, it is practical to determine if a correlation exists between symptoms and serum drug concentrations. A comparative study of human tolerance and bioavailability between the two available formulations has been done.

METHODS:

Subject Selection:

Male candidates 21 to 45 years of age were selected from applicants for temporary employment as study subjects.

Drug Administration:

A 2 x 2 balanced latin square crossover design was used in this study. Drug lots used and dosing schedules are on file.

Clinical, Laboratory and Drug Assay Schedules:

Serial comprehensive medical evaluations including physical, biochemical and hematologic testing were performed on each subject.

RESULTS:

Compliance:

One subject terminated participation for personal reasons and was not administered B512. Another was terminated because of pharyngitis six days after receiving B512 and did not receive E443. Therefore, 6 subjects completed the "crossover" as planned and 7 administrations of each formulation was accomplished. The two withdrawals did not affect the balance of the 2 x 2 latin square design since 3 subjects in each group, A & B, completed both parts of the study.

Symptoms and Physical Findings:

Administration of both formulations of WR 142,490-HCl as a single 1,750 mg oral dose was associated with combinations of mild and temporary nausea, abdominal cramps, and loose stools. Additionally, non-incapacitating lightheadedness occurred in four instances in 3 subjects: following administration of E443 on two occasions and B512 on two occasions.

Physical Examination:

Subject No. 204 developed pharyngitis and otitis externa accompanied by temporary enzyme elevation following B512 administration on Day 7 of the 1st study interval. Subject No. 206 developed a left otitis externa following a weekend at the beach. The physical abnormalities were not considered drug related.

Laboratory Tests:

Abnormal hematologic and biochemical values are tabulated and on file. There is no pattern suggesting the minor abnormalities observed were drug related. The following abnormalities warrant comment: Subject Code No. 204 developed pharyngitis, otitis externa and temporary elevation of SGPT, SGOT, and LDH 6 days following administration of B512 and was not administered E443. Urinalyses were abnormal on three occasions in 3 different subjects. Subject Nos. 203 and 207 had trace glucosuria and trace proteinuria respectively. Subject Code No. 208 developed temporary microscopic hematuria on Day 7 of the first study interval following trauma. Electrocardiographic rhythm strips did not change significantly in any subject following drug administration.

Individual Final Summaries:

Final summaries for each subject are on file.

CONCLUSION:

WR 142,490·HCl as formulated in Lots B512 and E443 are not tolerated at a single oral dose of 1750 mg as administered in this study. Intolerance was manifested by combinations of nausea, abdominal cramps, and loose stools. These symptoms were mild and temporary. Additionally, three subjects complained of non-incapacitating lightheadedness: one following administration of each formulation and one each following B512 and E443. It should be noted that the intolerance was not of sufficient magnitude to preclude use of the dose level and formulations as tested if the clinical need existed. In such an instance E443 appears to be preferable as the frequency and duration of symptoms were less than following administration of the B512 formulation.

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EXPERIMENT NO. 4: WR 142,490·HCl SAFETY AND TOLERANCE Repetitive Curative Dose Levels

STUDY SUMMARY

INTRODUCTION:

Mefloquine hydrochloride, WR 142,490, has been shown to be a highly effective antimalarial when administered as a single oral dose in humans ill with chloroquine resistant strains of P. falciparum. Twelve of fourteen non-immune subjects infected with chloroquine resistant strains of P. falciparum and administered mefloquine hydrochloride, were cured with single doses of 1.0-1.5 gm. Recrudescence occurred in the two remaining individuals, one of whom was cured with a repeat 1.0 gm dose of mefloquine.

Phase III mefloquine clinical studies, in Thailand, with naturally acquired P. falciparum infections appear promising. However, two recrudescences following treatment occurred. It is anticipated repeat dosing in individuals who recrudesce after initial clearing of parasitemia may be necessary.

This study was performed to determine tolerance and safety of WR 142,490·HCl, administered orally to healthy human subjects, when predicted curative single dose levels are repeated on the 7th day following initial dosing. A total of three consecutive rising dose levels were used in a double blind study. Four subjects participated at each dose level. The dose levels and assignment, to receive drug or placebo, are on file.

A capsule formulation had been used for most previous WR 142,490·HCl studies. For this study a more rapidly dispersing coated tablet formulation designated Lot B512 was used.

METHODS:

Subject Selection:

Male candidates 21 to 45 years of age were selected from applicants for temporary employment as study subjects.

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Drug Administration:

A double blind method was used. Drug lots administered and dosing schedules are on file.

Clinical, Laboratory and Drug Assay Schedules:

Serial comprehensive medical evaluations including physical, biochemical and hematologic testing were performed on each subject.

RESULTS:

Symptoms and Physical Findings:

One control subject (#89) had transient abdominal cramps and passed one loose watery stool thirteen hours after placebo administration.

Five of the six subjects receiving drug had gastrointestinal symptoms. At the 1000 mg dose level Subject #87 experienced transitory nausea followed by passage of a loose, brown, watery stool within the first hour after the first drug administration. Subject #85 tolerated both drug administrations and Subject #87 tolerated the second administration without any symptoms.

The symptoms at the 1250 mg dose level were more frequent and of longer duration. Although Subject #92 tolerated the second administration without symptoms, three watery stools were passed starting 30 minutes after the initial dosing and ending 180 minutes later. Subject #90 developed symptoms 30 minutes after each dosing including 3-5 watery stools during a 2-3 hour interval.

At the 1500 mg dose level, both subjects were intolerant of the drug each time it was administered. Subject #94 developed slight nausea and passed a watery stool 30 minutes after the initial dose. The nausea persisted for 1 hour. Following the second dose, nausea was absent, but the subject passed four watery stools during the interval of 60 minutes to 150 minutes after dosage. Subject #95 became nauseated 90 minutes following the initial dose immediately after breakfast and vomited the breakfast 30 minutes later. No loose stools were passed. Following the second administration of drug, nausea was absent but four watery stools were passed during the interval of 1½ hours to 3 hours after drug administration.

The description, onset, and duration of all symptoms and findings for the entire study group are on file.

Physical Examination:

No significant abnormalities developed during the study period.

Laboratory Tests:

There were no significant alterations in these tests attributable to drug ingestion.

Urinalyses:

There were no significant alterations in urine protein, glucose, or changes in urine sediment attributed to drug ingestion.

Electrocardiography and Phototoxicity:

No ECG rhythm changes were observed. Phototoxicity did not occur in the course of this study.

Individual Final Summaries:

Summaries for each subject are on file.

DISCUSSION:

Previous Phase I testing with mefloquine, Lot E443 (Lafayette Pharmacal, Inc.) in humans, at the Statesville Penitentiary, established that the drug was well tolerated in single oral doses of 2000 mg. However, in the present study a different formulation of WR 142,490·HCl, Lot B512 (INTERx, Inc.), was used. This formulation is designed as a more rapidly dispersing coated tablet as compared with the capsules and tablets used in most earlier clinical trials. Tolerance of the two formulations appears to be quite different.

Since only one control subject developed gastrointestinal symptoms following placebo ingestion, it is suggested that the symptoms observed in this study were induced by active drug or the combination of drug and excipient.

It should be noted that symptoms occurred in only 1 of 4 administrations of the 1000 mg dose. The frequency and duration of loose stools were approximately the same at the 1250 and 1500 mg dose level, but nausea and emesis occurred only at the 1500 mg dose level. It is undetermined whether or not the drug was returned in the one episode of emesis that occurred, but it may be inferred since diarrhea did not occur following that administration, but did occur following the second administration to that subject.

CONCLUSION:

Intolerance to the INTERx formulation of WR 142,490·HCl, designated Lot B512, occurred at the three dose levels tested. Intolerance was minimal at the lowest dose tested (1000 mg) and consistent at the highest (1500 mg). Intolerance was manifested primarily by passage of one to five watery stools starting 30 to 90 minutes after drug ingestion and lasting for $\frac{1}{2}$ to 3 hours. Mild nausea occurred in 3 of 12 trials. Emesis occurred once and may have included all or part of the administered drug. No other symptoms, physical or laboratory abnormalities of significance occurred in the subjects during the study.

RECOMMENDATIONS:

It is recommended that cross over investigations be performed between WR 142,490·HCl formulations for comparative tolerance and bioavailability.

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EXPERIMENT NO. 7: WR 180,409·H₃PO₄

SHORT TERM DOSAGE SAFETY AND TOLERANCE

RISING SINGLE DOSE LEVELS

STUDY SUMMARY

INTRODUCTION:

The study was performed to determine the short term dosage safety and tolerance of WR 180,409·H₃PO₄ administered orally to human subjects. A total of 11 study intervals were used to administer drug or placebo to 43 subjects. The dose levels and assignment to receive drug or placebo for each subject are on file.

SUBJECT:

Recruitment:

Subjects were healthy males aged 21 to 45 years, weighing between 50-100 kg. They were recruited from the Washington, D.C. metropolitan area and were hired as temporary employees.

Screening:

Candidates for employment underwent qualifying examinations to obtain the subjects for study. The initial evaluation included a complete history and physical examination, chest x-ray, electrocardiogram and the following tests: urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, Na⁺, K⁺, Cl⁻, CO₂, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin. Laboratory tests were performed by National Health Laboratories, Incorporated using standard methods. Chest x-rays were performed in the Department of Radiology at the Washington Hospital Center. Electrocardiograms were performed by trained personnel using a Cambridge VS-4 portable electrocardiograph machine. Urinalyses were performed in the research unit laboratory using standard methods.

Informed Consent:

Qualified candidates were presented with a complete explanation of the background and rationale for the study as well as procedures to be used. Candidates were interviewed as a group and individually. At individual interviews it was ascertained the candidate understood the study and personal risk factors. Qualified candidates were asked to read and permitted to sign the consent statement.

Human Use Committee:

The committee is composed of individuals from the community including previous subjects. A member of the Human Use Committee participated in the consent interviews and made frequent visits to the research unit to monitor the study and assure the subjects' health and welfare were given primary consideration. Each subject clearly understood that he could terminate his participation in the study at any time.

HOUSING:

Subjects were housed in the clinical research unit of the Washington Hospital Center, utilizing semi-private rooms with modern facilities. A lounge area was available which contained television, reading materials, games, chairs, and desks. Subjects, supervised by the investigating team, were allowed to use the tennis courts, swimming pool and recreational facilities of the Washington Hospital Center. Each subject underwent serial physical examinations in the unit examining room and special tests were performed in specialty areas within the hospital.

METHODS:

Drug administration:

Drug lots used, dosing schedules, number of subjects in each study period and incremental increases in doses are on file. Twenty-two subjects received drug and 21 placebo.

Clinical and laboratory evaluations:

Serial comprehensive medical evaluations including physical, biochemical and hematologic testing were performed on each subject.

RESULTS:

Symptoms and physical findings:

The two subjects receiving 1500 mg and 3 of the 4 subjects receiving 1250 mg as well as 3 of the 4 receiving 1000 mg had symptom patterns suggestive of intolerance including combinations of nausea, vomiting, light-headedness, mental fuzziness and inability to concentrate. In all subjects the symptoms were mild, not incapacitating and of less than 48 hours duration.

Physical examinations:

No abnormalities occurred during the course of the study which were attributable to participation in the study.

Laboratory tests:

Subject #160 receiving 1250 mg WR 180,409-H₃PO₄ was reported to have 10,000 platelets on a blood specimen drawn approximately 22 hours after drug ingestion. There was no associated purpura or petechiae produced with the tourniquet test and repeat platelet counts 44 hours after drug ingestion were normal. This finding is possibly but not probably drug related. Only 4 of the 43 subjects were without at least one abnormal laboratory value in the hematologic or biochemical testing. The abnormalities observed were random, inconsistent or marginal. None of the abnormal values reported except as noted above were considered possibly drug related.

Urinalysis was normal at all times and in all subjects except for the following: Subject #124 receiving 5 mg drug had 9 WBC's per high powered field in the urinary sediment on day 3 only. Subject #161 receiving 1000 mg of drug had pyuria day 3 of 27 WBC's per high powered field and on day 7, 7 WBC's per high powered field. The urinalysis on the days of pyuria were otherwise normal and were completely normal on all other test days. The intermittent pyuria observed is not attributed to drug ingestion as it has been seen during previous studies with equal frequency in both drug and placebo administered subjects.

Individual Summary Forms:

Individual summary forms for each subject are on file.

CONCLUSION:

It was concluded that intolerance to single dose oral administration of WR 180,409·H₃PO₄ was manifested by combinations of nausea, vomiting, light-headedness and mental fuzziness. Intolerance was marginal at the 750 mg dose and definite but not universal at the 1250 mg dosage. The two subjects receiving 1500 mg both had multiple symptoms of intolerance. In no instance was the intolerance incapacitating and it was of less than 36 hours duration in all subjects.

RECOMMENDATIONS:

WR 180,409·H₃PO₄ is well tolerated in single oral dose administration at dose levels which may be efficacious. The intolerance manifestations to the drug are mild and not incapacitating. Therefore, it is recommended that bioavailability studies following single dose oral administration be performed.

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